REMARKS

Claims 33-44 are pending.

In a prior Office Action, dated February, 22, 2002, the Examiner stated that Applicants must file a request for interference under 37 C.F.R. §§ 1.607 and 1.608(b) in order to have an interference declared with Trinchieri's Patent No. 5,811,523 ("'523 patent"). Applicants complied, and filed their Request on January 23, 2003 ("Request").

In the outstanding Office Action, dated June 12, 2003 ("Office Action"), the Examiner objected to certain claims on the ground that they were duplicative of other claims. The Examiner also maintained rejections of all claims for anticipation by and obviousness over the '523 patent based on the Examiner's conclusion that the '523 patent is entitled to the November 10, 1988 filing date of Trinchieri's parent application Serial No. 269,945 ("'945 application") and, therefore, is prior art under Section 102(e) against the captioned application. Thus, Applicants' request for interference has been held in abeyance pending resolution of the objection and the rejections based on the '523 patent. Office Action, p. 4, ll. 1-2.

Consequently, this Response is directed only to the objections and the rejections based on the '523 patent.

I. THE OBJECTION TO CLAIMS 35-38 AND 41-44

Claims 35 and 36 have been objected to under 37 C.F.R. § 1.75 as being substantial duplicates of claims 37 and 38, respectively. Claims 41 and 42 have been objected to under 37 C.F.R. § 1.75 as being substantial duplicates of claims 43 and 44, respectively. The Examiner stated:

> When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper *after allowing one claim* to object to the other as being a substantial duplicate of the *allowed* claim. MPEP.. § 706.03(k) (emphasis added).

Office Action, p. 2.

First, Applicants note that none of the claims that are subject to the objection have been allowed. Thus, according to the MPEP and the Office Action itself, the objection is not ripe to be made.

Second, the pairs of allegedly duplicative claims are not duplicates because they contain different limitations. More importantly, however, the pairs of Applicants' claims differ from each other *in exactly the same way corresponding pairs of claims in the Trinchieri '523 patent differ from each other.* The table below reflects the general correspondence of claims:

Captioned Application	Trinchieri '523 Patent
35	2
36	3
37	6
38	7
41	2
42	3
43	6
44	7

Claims 2 and 6 of the Trinchieri '523 patent differ from each other in the same way claims 35 and 37 of the captioned application differ from each other. Specifically, claim 2 of the '523 patent is directed to an antibody of claim 1 wherein the antibody reacts with the first subunit of IL-12, and wherein *specific* amino acid sequences are recited for *both* subunits (in view of its dependency from claim 1). Claim 6 of the '523 patent is also directed to an antibody which specifically reacts with the first subunit of IL-12; however, in contrast to claim 2, claim 6 does not recite a specific sequence for the second, 30-35 kD subunit.

Similarly, claim 35 of the captioned application is directed to a monoclonal antibody of claim 33 wherein the monoclonal antibody reacts with the first subunit of IL-12, and wherein *specific* amino acid sequences are recited for *both* subunits (in view of its dependency from claim 33). Claim 37 of the captioned application is also directed to a monoclonal antibody which specifically reacts with the first subunit of IL-12; however, in contrast to claim 33, claim 35 does not recite a specific sequence for the second, 30-35 kD subunit.

In the same fashion, claim 41 of the captioned application is directed to an isolated antibody of claim 39 wherein the isolated antibody reacts with the first subunit of IL-12, and wherein *specific* amino acid sequences are recited for *both* subunits (in view of its dependency from claim 39). Claim 43 of the captioned application is also directed to an isolated antibody which specifically reacts with the first subunit of IL-12; however, in contrast to claim 41, claim 43 does not recite a specific sequence for the second, 30-35 kD subunit.

Claims 3 and 7 of the Trinchieri '523 patent differ from each other in the same way claims 36 and 38 of the captioned application differ from each other. Specifically, claim 3 of the '523 patent is directed to an antibody of claim 1 wherein the antibody reacts with the second subunit of IL-12, and wherein *specific* amino acid sequences are recited for *both* subunits (in view of its dependency from claim 1). Claim 7 of the '523 patent is also directed to an antibody which specifically reacts with the second subunit of IL-12; however, in contrast to claim 3, claim 7 does not recite a specific sequence for the first, 40 kD subunit.

Similarly, claim 36 of the captioned application is directed to a monoclonal antibody of claim 33 wherein the monoclonal antibody reacts with the second subunit of IL-12, and wherein *specific* amino acid sequences are recited for *both* subunits (in view of its dependency from claim 33). Claim 38 of the captioned application is also directed to a monoclonal antibody which specifically reacts with the second subunit of IL-12; however, in contrast to claim 33, claim 38 does not recite a specific sequence for the second, 40 kD subunit.

In the same fashion, claim 42 of the captioned application is directed to an isolated antibody of claim 39 wherein the isolated antibody reacts with the second subunit of IL-12, and wherein the *specific* amino acid sequences are recited for *both* subunits (in view of its dependency from claim 39). Claim 44 of the captioned application is also directed to an isolated antibody which specifically reacts with the first subunit of IL-12; however, in contrast to claim 42, claim 44 does not recite a specific sequence for the second, 40 kD subunit.

The pairs of Applicants' claims objected to reflect the same differences found in corresponding pairs of claims in the Trinchieri '523 patent, which were allowed by the same Examiner as here. It would therefore be manifestly unfair for the Examiner to refuse such claims to Applicants where she allowed those claims in the patent with which Applicants seek an interference.

Moreover, all of Applicants' claims have been presented for purposes of (i) satisfying the one year bar requirement of 35 U.S.C. § 135(b) and (ii) presenting claims to the "same patentable invention" as in corresponding pairs of claims of the '523 patent. Applicants cannot predict whether any differences in the corresponding claim pairs (claim 2 vs. claim 6; claim 3 vs. claim 7) of the '523 patent are "material" such that, absent copying *both* claims, the PTO may find that Applicants have not met the one year time bar as to claims not copied or that Applicants have not copied all Trinchieri's claims to the same patentable invention.

Given that the PTO has allowed pairs of claims in the Trinchieri '523 patent that Applicants *differ in exactly the same way* as corresponding pairs of claims in this application, and the PTO raises those *very same Trinchieri claims* as impediments to allowance of Applicants' claims, the PTO should not object to Applicants' corresponding claims as "duplicative." Applicants respectfully request that the objection be withdrawn.

II. THE REJECTION FOR ANTICIPATION UNDER SECTION 102(e) BY THE DISCLOSURE OF THE TRINCHIERI '523 PATENT

Claims 33-44 have been rejected as anticipated under 35 U.S.C. § 102(e) by the disclosure of the Trinchieri '523 patent. For purposes of organizing this Response so as to address each of the arguments presented in the Office Action, Applicants quote from the Office Action and present their rebuttal immediately following each quotation. Near the end of this Response, Applicants list the arguments presented in their Request that were not discussed by the Examiner.

A. The Examiner's Conclusion That The '523 Patent Is Entitled To A Date Prior To Applicants' Effective Date Is Fundamentally Flawed

The Office Action states (at p. 3):

> Applicants argue that they seek, pursuant to 37 C.F.R. §§ 1.607 and 1.608(b) to provoke an interference between the instant application and U.S. Patent No. 5,811,523. However, contrary to Applicants arguments, the position of the Office is that the 35 U.S.C. 102(e) rejection over claims 33-44 as being anticipated by Trinchieri et al. (US Patent No. 5,811,523), is being maintained. The crucial issue here is that the priority date for US Patent No. 5,811,523, is 11/10/1988, which is *the earliest application that describes partial amino acid sequences of the protein* and the biological activity of the protein. Furthermore, the declaration of Dr. William R. Benjamin is non-persuasive because it fails to demonstrate (1) the '523 patent is not entitled to its earliest filing date of 11/10/88 and (2) diagnostic and therapeutic uses of the claimed antibodies are not a specific utility. Therefore, an interference with U.S. Patent No. 5,811,523 and the instant application cannot be declared at this time (emphasis added).

The above introduction to the Office Action highlights the major difference between Applicants' position and the Examiner's position. The Examiner concludes that the '523 patent is entitled to an effective date of November 10, 1988, the date the '945 application was filed, while Applicants dispute this conclusion.

While the Examiner *admits* in this introduction that the '945 application describes only *partial* amino acid sequence data for the two subunits of IL-12, the Examiner

nonetheless accords Trinchieri benefit of that application for all claims, despite that all claims recite the *complete* amino acid sequence of at least one subunit.[1] This is a fundamental and reversible error. The Examiner's action is contrary to established case law under which the *written description requirement* can only be met for a claim reciting an amino acid sequence if the *complete* amino acid sequence is disclosed. See, for example, *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ2d 1398 (Fed. Cir. 1997), *cert. denied*, 510 U.S. 1140 (1998) (finding no written description of a claim reciting "human insulin DNA" because "[n]o sequence information indicating which nucleotides constitute human cDNA appears in the patent"); *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) ("an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."); see also Applicants' Request, pp. 27-28. The Examiner has not presented any reasoning or cited any case law to support her position that an application *lacking* the complete amino acid sequence of a protein provides a *written description* for a claim that recites the entire amino acid sequence.

A second fundamental error is the Examiner's conclusion that Trinchieri's bare description of "diagnostic and therapeutic uses," *with absolutely no disclosure of what condition or disease can be diagnosed or therapeutically treated*, is a specific utility sufficient to meet statutory requirements. This position is contrary to established case law, such as *In re Brana*, 51 F.3d 1560, 1564-65, 34 USPQ2d 1436, 1440 (Fed. Cir. 1995), and contrary to the PTO's own "Guidelines for Examination of Applications for Compliance with the Utility Requirement," 66 Fed. Reg. 1092, 1097-99 (Jan. 5, 2001). See Applicants' detailed legal analysis in their Request, pp. 28-33. The Examiner has not identified in the '945 application a single condition or disease that can be diagnosed using the claimed antibodies or a single condition or disease that can be therapeutically treated with those antibodies. Absent disclosure of any such specific condition or disease in the '945 application, Trinchieri is not entitled to the November 10, 1988 date.

Thus, the two legal bases on which the Examiner rejected Applicants' attack on Trinchieri's entitlement to benefit of the '945 application are clearly faulty under the law

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[1] That the complete sequence of each recited subunit constitutes a material limitation in Trinchieri's claims is shown in Applicants' Request, at pp. 8-9, which cites to the file history of the '523 patent and shows that the Examiner allowed the claims only after Trinchieri complied with the Examiner's requirement that the claims recite the full amino acid sequence of any recited subunit.

of written description and utility. These issues will be discussed in greater detail later in this Response.

B. Applicants' Written Description And Enablement Attacks On Trinchieri's Right To Benefit Of The '945 Application Are Based On Actual Data In Applicants' Specification And Two Publications, Which The Examiner Has Not Rebutted

The Office Action states (p. 4):

> Applicants argue that only by using special techniques was it possible for Applicants to generate the antibodies that specifically react with the 30-35 kD subunit (Example 14, pages 79-80). Applicants also argue that none of the 20 monoclonal anti-CLMF antibodies produced from immunization with *partially purified* 75 kD heterodimeric CLMF bind to the 30-35 kD subunit. In support of this conclusion, Applicants have cited D'Andrea et al and Chizzonite et al., which are scientific publications from 1991 (emphasis added).

The above paragraph addresses Applicants' position that the Trinchieri '523 patent is not entitled to the filing date of the '945 application for Trinchieri's claims that encompass antibodies that "specifically react" with the 30-35 kD subunit, namely, Trinchieri's claims 1, 3-5 and 7.[2]

1. Applicants Argued That The '945 Application Lacks Both Enablement *And Written Description* For Antibodies To The 30-35 kD Subunit

Applicants' Request, at pp. 35-39, focused on the failure of the '945 application to provide a written description of an enabling method to make the 30-35 kD subunit. Thus, the proper *legal* context is *both enablement and written description*. Note that the title of Section D at p. 35 of Applicants' Request reads: "The '945 Application *Fails To Describe* How To Make Antibodies To The 30-35 kD Subunit, So There Can Be *No Written Description Or Enablement* For Proposed Count B" (emphasis added). Throughout the Office Action, it would appear that the Examiner has considered only enablement and ignored Applicants' written description attack. Nevertheless, the '945 application fails to meet both requirements.

All of this discussion revolves around whether the one and only sentence in the '945 application describing antibodies to IL-12 is sufficient to meet the enablement *and* written description requirements. That sentence reads:

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[2] Clearly, claim 1 encompasses such subject matter because claim 3, which depends from claim 1, recites antibodies that specifically react with the 30-35 kD subunit.

> Other uses for these novel [IL-12] polypeptides are in the development of monoclonal and polyclonal antibodies generated *by standard methods* for diagnostic or therapeutic use.

'945 application, p. 18, ll. 14-17 (emphasis added). *This is the sole disclosure in the '945 application relating to antibodies and their uses.*

2. <u>The Legal Standards For Written Description And Enablement</u>

Section 112 sets forth the requirements for written description and enablement. These dual requirements were highlighted in *In re Barker*, 559 F.2d 588, 593, 194 USPQ 470, 474 (C.C.P.A. 1977):

> Accordingly, we reaffirm our recognition that 35 U.S.C. § 112, first paragraph, contains separate requirements for --
>
> > a written description [1] of the invention, and [2] of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . . .

Therefore, Section 112 requires both (1) a *written description* of the invention and (2) a *written description* of how to make and use that invention that is sufficient to *enable* one skilled in the art to practice the invention.

To satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an application must describe the invention such that a person skilled in the art would clearly conclude that the applicants invented the claimed invention. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied*, 510 U.S. 1140 (1998). In evaluating the written description requirement in the context of a claim reciting DNA, the Court in *Lilly* found:

> An adequate written description of a DNA . . . "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention." *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 U.S.P.Q.2D (BNA) 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. *Id.* at 1170, 25 U.S.P.Q.2D (BNA) at 1606.

Lilly, 119 F.3d at 1566-67, 43 USPQ2d at 1404. With respect to claims reciting a "human insulin cDNA," the Court held that, while the patent contains a description of a general method of producing human insulin cDNA and a description of the human insulin A and B chain amino acid sequences that the cDNA encodes, *it does not provide a written description of human insulin cDNA itself*" (emphasis added). *Lilly*, 119 F.3d at 1567, 43 USPQ2d 1405.

Also involved in *Lilly* were generic claims reciting mammalian and vertebrate insulin cDNAs. The only such cDNA for which there was structural information (*i.e.*, full nucleotide sequence) in the patent was rat insulin cDNA. The Court found that such generic claims were not described by the general language of the patent that was supported only by the specific nucleotide sequence of rat insulin cDNA. *Lilly*, 119 F.3d at 1569, 43 USPQ2d 1406. Thus, claims requiring "human," "vertebrate" or "mammalian" insulin cDNA were held invalid.

To satisfy the enablement requirement, a patent application must describe how to make the claimed invention in sufficient detail so that the application would permit one skilled in the art to practice the invention at the time of filing without undue experimentation. See *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997).

Whether a claimed invention is enabled under Section 112 is a different question of law that is based upon several underlying factual inquiries. *See, e.g., Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1742 (Fed. Cir. 1987). A number of factors have been considered in determining what constitutes undue experimentation. The decision in *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Interf. 1986), summarizes the "ultimate question" in enablement determinations:

> The *ultimate question* in each case of this type is whether or not the specification contains a *sufficiently explicit disclosure* to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (emphasis added). In *Wands*, the Court listed the factors to be considered in the enablement analysis:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. (footnote omitted). *All* of the listed factors set forth in *Forman* and *Wands* need *not* be considered in determining whether the application is sufficient since they are illustrative, not mandatory. *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991). An application may be found non-enabling based solely on an evaluation of the amount of direction or guidance presented. *See, e.g., Genentech,* 108 F.3d at 1366, 42 USPQ2d at 1004-05 (Fed. Cir. 1997).

The Court in *Genentech* held that such a failure to provide sufficient guidance "cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art." 108 F.3d at 1366, 42 USPQ2d at 1005. The court emphasized that the application must describe how to practice the invention:

> Genentech's arguments, focused almost exclusively on the level of skill in the art, ignore the essence of the enablement requirement. Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 86 S. Ct. 1033, 16 L.Ed.2d 69, 148 U.S.P.Q. 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure.

Genentech, 108 F.3d at 1366, 42 USPQ2d at 1005.

As further noted by the Court, while not every detail necessary to make the invention need be disclosed, an inventor cannot simply rely on what one skilled in the art could do to meet the requirement for an enabling disclosure:

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement.*

108 F.3d at 1366, 42 USPQ2d at 1005 (emphasis added). Thus, a defective application that fails to describe how to make the claimed invention cannot be remedied by reference to methods known in the art. A description of an enabling method of making the invention must be in the application itself.

Accordingly, no matter what state-of-the-art reference may be raised by the Examiner, it cannot be used to establish that the '945 application itself describes how to make the claimed invention. An enabling description must be in the '945 application itself in order for the application to meet the enablement requirement. It is not. Therefore, the '945 application fails, as a matter of law, to satisfy the enablement requirement of Section 112 for

Trinchieri's claims 1, 3-5 and 7, and Trinchieri is not entitled to benefit of the filing date of that application for those claims.

Applicants' Request presented facts from their own specification, the D'Andrea *et al.* publication, the Chizzonite *et al.* publication and the Benjamin Declaration, on which Applicants' base their positions that:

(i) "Standard methods" known in the art as of the filing date of the '945 application would not have produced in antibodies that "specifically react" with the 30-35 kD subunit. Therefore, the '945 application *fails to enable* a method for making such antibodies.

(ii) The'945 application must contain a written description of a method make such antibodies because a failure to provide sufficient guidance cannot be rectified by asserting that all the disclosure related to the method that subsequently worked is within the skill of the art. However, the '945 application fails to state anything more than to use "standard methods" so it *fails to provide a written description* of how to make such antibodies.

3. The Examiner Has Not Considered The Actual Data In Applicants' Specification

Applicants relied on *actual data* in their specification to demonstrate that "standard methods" do not result in antibodies that specifically react with the 30-35 kD subunit. That data is discussed at pp. 35-36 of the Request:

> However, Applicants' use of that "standard method" did not result in the production of polyclonal antibodies within the scope of proposed count B. The data in Applicants' specification (p. 73, l. 20 to p. 74, l. 9) demonstrates that all of the 20 monoclonal anti-CLMF antibodies produced from immunization with *partially purified* 75 kD heterodimeric CLMF (a) bind specifically to the non-reduced 75 kD CLMF heterodimer and (b) bind specifically to the non-reduced 40 kD subunit ("all the monoclonal antibodies were specific for the 40 kDa subunit of CLMF") (p. 74, ll. 7-9). Since the technique for making those monoclonals involves random selection from all antibodies in the polyclonal serum, any such polyclonal preparation would have antibodies that react with the 40 kD subunit. Thus, one would not obtain a polyclonal antibodies that specifically react with the 30-35 kD subunit. And without such polyclonal antibodies, one would not expect to isolate antibody-producing cells to fuse to myeloma cells to make hybridomas for the production of monoclonal antibodies that specifically react with the 30-35 kD subunit (emphasis added).

As is evident from the Examiner's introduction above (Office Action, p. 4), the Examiner has not responded to Applicants' data.[3] Rather, the Examiner immediately looked to two references, D'Andrea *et al.* and Chizzonite *et al.*, which Applicants presented as *additional* support for Applicants' position. In addition to considering these references, the Examiner is requested to analyze the data in Applicants' application on the issue.

4. D'Andrea *et al.* Also Shows That The '945 Application Lacks Enablement And Written Description For A Method Of Making Antibodies That Specifically React With The 30-35 kD Subunit

In addition to the data in their specification, Applicants relied on portions of the D'Andrea *et al.* publication to support their position that the '945 application does not enable production of antibodies that specifically react with the 30-35 kD subunit. Specifically, in their Request, Applicants stated:

> The results in D'Andrea *et al.* show that antibodies generated against recombinantly produced NKSF heterodimer (referred to in D'Andrea *et al.* as "C11" antibodies) fail to react with the 30-35 kD NKSF subunit and exhibit a reactivity pattern similar to antibodies generated against just the NKSF 40 kD subunit (referred to in D'Andrea *et al.* as the "C8 series" of antibodies), *i.e.*, only react with the 40 kD subunit (D'Andrea *et al.*, p. 1390, left column, and Fig. 1).

Request, p. 20 (emphasis added).

Despite that *recombinant produced* IL-12 was not available as of the November 10, 1988 filing date of the '945 application,[4] Applicants summarized in the preceding quotation certain data reported by D'Andrea *et al.* that was derived from such recombinant material. In explaining why they referenced D'Andrea *et al.*, Applicants first note that purified natural IL-12 heterodimer (70 kD) contains excess free 40 kD subunit, as discussed in the Benjamin Declaration, dated January 17, 2003, ¶¶ 16 and 17:

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[3] The antigen used to generate antibodies in this portion of Applicants' specification was *partially purified natural* IL-12. This "partially purified 75 kD heterodimeric CLMF" was natural material derived from cells that normally produce the heterodimeric protein; it was not recombinantly produced. This is clear because Applicants generally distinguished in the captioned application between purified natural material, which they referred to as "purified or partially purified CLMF," and material expressed recombinantly, which they referred to as "recombinant CLMF." See, for example, reference to "natural CLMF is obtained in pure form" at p. 12, lines 28-29, and the use of "recombinant CLMF" at p. 69, line 19, to refer to the material produced in COS cells. See also, "Human rIL-12 was produced from cotransfection of COS cells . . . " at p. 83, line 20, where "rIL-12" clearly refers to recombinant IL-12.

[4] Importantly, the D'Andrea *et al.* publication was published in 1992, over three years after Trinchieri filed the '945 application on November 10, 1988.

16. Conditions that stimulate production of biologically active NKSF heterodimer also induce production of a large excess free 40 kD NKSF subunit. See, e.g., Chizzonite et al., p.1555, paragraph bridging left and right columns; and D'Andrea et al. (Exhibit 4), Figs. 4A-4B, p. 1392, and accompanying text. . . .

17. The '945 application discloses a method that purports to partially purify IL-12 (see, for example, '945 application, p. 21, l. 12, to p. 24, l. 20). Note, however, that the *free 40 kD subunit is present in excess in biological samples, and is also present in the partially purified IL-12 preparation described in the '945 application.* Any such partially purified IL-12 preparation containing excess free 40 kD subunit, if used to elicit antibodies, would result in antibody preparations against both the free 40 kD subunit and IL-12. . . . (emphasis added).

In referring to antibodies generated using *recombinantly produced* IL-12 heterodimer in their Request, Applicants were making the point that the specificity of these antibodies was consistent with the expected specificity of antibodies that were generated against *partially purified natural* IL-12 heterodimer. Thus, Applicants noted that antibodies generated against recombinantly produced IL-12 heterodimer (the "C11" antibodies of D'Andrea *et al.*) fail to react with the 30-35 kD subunit and, in fact, reacted only with the 40 kD subunit, a reactivity pattern similar to that of antibodies raised against partially purified natural IL-12 heterodimer. Again, Applicants made this point to support their position that one cannot make antibodies that specifically react with the 30-35 kD subunit using partially purified natural IL-12 because standard techniques would result in antibodies that specifically react with the 40 kD subunit, not the 30-35 kD subunit.

5. The Data Relied On By The Examiner From D'Andrea *et al.* Utilizes Recombinantly Produced Materials That Were Not Available As Of Trinchieri's November 10, 1988 Filing Date

The Office Action states (pp. 4-5):

Applicants argue that the results in D'Andrea et al show that antibodies *generated against recombinantly produced NKSF heterodimer* fail to react with the 30-35 kD NKSF subunit and react only with the NKSF 40 kD subunit. However, contrary to Applicants' arguments, the reference discloses that the C2 and C3 series of mABs *generated using E. coli-derived p40 chain* as antigen, react with both E. coli-derived and Cos-derived p40 as well as with CHO-derived p70 (see page 1390, column 1, see first full paragraph, specifically lines 9-13). The C8 series of antibodies, *generated using as antigen Cos-derived p40* react with Cos-derived p40 and CHO-derived p70 but nor [sic, not] E. coli-derived p40 (see page 1390, column 1, lines 13-16). The reference also discloses that antibodies *generated using as antigen E. coli-derived p35* react with E. coli derived p35 and with the

> p70 heterodimer but not with the p40 preparation (see page 1390, column 1, lines 19-22). The reference discloses that the antibodies *against CHO-derived p70* react with p40 but no data is shown and the reactivity of the antibody with p35 is not mentioned, which does not reach the conclusion that there is not reactivity of this antibody with the p35 subunit (see page 1390, column 1, lines 17-19) (emphasis added).

Applicants have argued that antibodies generated using "standard methods" against *purified natural IL-12 heterodimer* (*i.e.*, using *purified natural IL-12 heterodimer* as the antigen) will not react with the 30-35 kD subunit. The Examiner's statements of the quotation, on the other hand, relate to antibodies generated using (1) *E. coli*-derived p40, (2) Cos-derived p40, (3) *E. coli*-derived p35 and (4) CHO-derived p70. Each of these four antigens used to produce the antibodies referred to by the Examiner is recombinantly produced.

As noted, Applicants' relied on the specificity data for antibodies generated using CHO-derived p70 to illustrate that the same reactivity profile was obtained for antibodies generated using purified natural IL-12 heterodimer (70 kD).[5] Note, however, that whatever the properties of antibodies generated using *any* recombinantly produced IL-12

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[5] Applicants challenge the Examiner's attack on the data from D'Andrea *et al.* concerning the properties of antibodies generated using recombinantly produced p70 heterodimer. The Examiner stated (Office Action, pp. 4-5):

> The reference discloses that the antibodies against CHO-derived p70 react with p40 *but no data is shown and the reactivity of the antibody with p35 is not mentioned*, which does not reach the conclusion that there is not reactivity of this antibody with the p35 subunit (see page 1390, column 1, lines 17-19) (emphasis added).

First, D'Andrea *et al.* state, at p. 1390, column 1, lines 17-19:

> The C11.5 and C11.79 antibodies, generated against CHO-derived p70, react with the p40 chain and have a reactivity similar to that of the C8 series (not shown).

D'Andrea *et al.* clearly state that these "C11" antibodies have a reactivity similar to that of the "C8" series. As noted in the sentence immediately preceding the quoted one (*i.e.*, p. 1390, column 1, lines 13-16) and shown in Figure 1 part "A", the "C8" antibodies *do not react with E. coli p35*. Therefore, the "C11" antibodies, "which have a reactivity similar to that of the C8 series," do not react with *E. coli* p35 either. The Examiner cannot ignore D'Andrea *et al.*'s result on grounds that the authors chose to state the result without showing the actual data (after all, it was accepted by the journal's editors). Further, contrary to the Examiner's statement, the reactivity of the "C11" antibody with p35 *is mentioned* in D'Andrea *et al.* because the authors stated that the "C11" antibodies had a reactivity "similar to that of the series," for which data is shown in Figure 1 part A that they do not react with *E. coli* p35.

subunit, or the recombinantly produced IL-12 heterodimer, *those materials were not available or enabled in the '945 application*. Thus, those materials *cannot* be used to demonstrate that Trinchieri's '945 application were enabling as of November 10, 1988.[6]

Applicants correctly addressed the issue of how to make antibodies using materials that were described in Trinchieri's '945 application or available in the art as of the November 10, 1988 filing date of the'945 application. It was only partially purified natural IL-12 that was disclosed in the '945 application or available as of that November 10, 1988 date. This is evident from simply reading the '945 application itself; there is no disclosure of any recombinant clone having DNA sequences encoding either of the two subunits of IL-12. Thus, the application could not have enabled the recombinant production of either subunit.

Clearly, the above quotation from the Office Action refers to generating antibodies using recombinant materials that were *not* available in the art as of November 10, 1988 and *not* described in the '945 application. Consequently, whatever antibodies could be produced with the recombinantly produced proteins is not relevant to what would have been produced as of the November 10, 1988 date using *partially purified natural* IL-12 since the recombinantly produced materials were not enabled as of that date, as the Examiner has argued.

6. Chizzonite *et al.* Also Shows That The '945 Application Lacks Enablement And Written Description For A Method Of Making Antibodies That Specifically React With The 30-35 kD Subunit

The Office Action states (p. 5):

> With respect to the Chizzonite et al reference, Applicants argue that the results presented demonstrate that using purified NKSF resulted only in generating antibodies which specifically bind the 40 kD subunit (page 1554, left column). However, contrary to Applicants arguments, the reference discloses that the anti-IL-12 serum and anti-IL-12 mAb had a preference for the 40 kD subunit (see page 1554, column 1, first three lines of second full-para). The reference does not teach away from the conclusion that the anti-IL-12 serum can also react with the p35 subunit i.e. that antibodies to the p35 subunit can also be obtained. A lot more hybridomas may have to be screened to get anti-IL-12 antibodies that react with the p35 subunit. Furthermore, Chizzonite et al point out that the apparent preference for antibodies directed against the 40 kD subunit, may be because significant amounts of free 40 D subunit are present in purified IL-12 samples which can bias toward identification of antibodies against the 40 kD subunit (see page 1555, left column).

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[6] Again, the D'Andrea *et al.* publication was not published until 1992, long after the filing date of the '945 application.

Applicants have also presented data from the Chizzonite *et al.* publication which shows that when antibodies were generated using purified or partially purified IL-12, *only* antibodies that specifically reacted with the 40 kD subunit were initially identified (Chizzonite *et al.*, p. 1554, left column, second full paragraph, last three lines):

> These data demonstrated that all the mAb [monoclonal antibodies] were specific for the 40-kDa subunit of IL-12.

In addition, at p. 1555, left column, third full paragraph, first sentence, Chizzonite *et al.* expressly state:

> Antibodies specific for the 35-kDa subunit were not isolated during the initial screening that identified 20 antibodies capable of immunoprecipitating [^{125}]IL-12.

As stated by Dr. Benjamin, no antibodies were produced in the initial screening which specifically react with the 30-35 kD subunit. Benjamin Dec., at ¶ 14.

Thus, the Chizzonite *et al.* paper *and* the Benjamin declaration expressly state that no antibodies were initially produced that specifically react with the 30-35 kD subunit.

The Examiner has provided no evidence to the contrary. Instead, the Examiner contends, *without supporting evidence*, that Chizzonite *et al.* merely shows a "preference" for obtaining antibodies that specifically react with the 40 kD subunit, as opposed to antibodies that specifically react with the 30-35 kD subunit. However, there is no evidence that antibodies that specifically react with the 30-35 kD subunit could be generated at all using the available purified natural IL-12 heterodimer preparations.

The Examiner further *speculates* that "[a] lot more hybridomas may have to be screened to get anti-IL-12 antibodies that react with the p35 subunit." Speculation, however, cannot serve as evidence. The fact of record is that no antibodies against the 30-35 kD subunit were initially isolated. No amount of speculation can change that fact.

Finally, the Examiner notes that Chizzonite *et al.* pointed out several possibilities that, in combination, may explain why no antibodies that specifically react with the 30-35 kD subunit were obtained (Chizzonite *et al.*, at p. 1555, left column):

> 1) the [^{125}]IL-12 preparation used during the initial screening assay contained significant amounts of free [^{125}]40-kD subunit that biased the screen to identify 40-kD specific antibodies; 2) the 35-kD subunit is much less immunogenic than the 40-kD subunit.

There is no need to debate the merits of this explanation. *Whatever the explanation for the result*, Chizzonite *et al.* proves that standard techniques employing purified natural IL-12 preparations available as of Trinchieri's November 10, 1988 filing date do not generate

antibodies that specifically react with the 30-35 kD subunit. And there is no written description in the '945 application of how to overcome this problem.

7. The Examiner's Speculation That "Multiple Immunizations" Would Have Been Performed Until Antibodies To The 30-35 kD Subunit Were Obtained Does Not Withstand Scruitiny

The Office Action states (pp. 5-6):

> Chizzonite et al. also reports that apparently antibodies against the 35 kD subunit arise only after "multiple immunizations" as opposed to antibodies against the 40 kD subunit which arise very rapidly (see page 1555, left column, last para). *If multiple immunizations was the state of the prior art at the time of the earliest priority date of the Trinchieri '523 patent*, the initial Trinchieri application (filing date, 11/10/88) was enabling for antibodies to the 35 kD subunit because not only the disclosure of the specification but the state of the prior art at the time an application is filed, is considered in determining whether a specification is enabling. The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification. Therefore, the state of the prior art evaluated at the time of the earliest Trinchieri application supports the conclusion that multiple immunizations with the 75 kD heterodimer would have resulted in the production of antibodies to the p35 subunit and the application would have been enabling for the claimed Trinchieri '523 invention (emphasis added).

Applicants acknowledge that Chizzonite *et al.* reported in 1991 that antibodies that specifically react with the 30-35 kD subunit were ultimately obtained, but "only after multiple immunizations." The Examiner concluded that "*If* multiple immunizations was the state of the art" on November 10, 1988 when the '945 application was filed, then that application was enabled.

Applicants have already submitted evidence with their Request showing that under the facts here, one skilled in the art would *not* have performed those multiple immunizations as of the November 10, 1988 date:

> 15. The techniques required by Chizzonite *et al.* to generate antibodies against the 30-35 kD subunit are not standard techniques that would have been utilized by one of skill in the art. Rather, using standard techniques, one skilled in the art, upon observing that immunized animals produced a sufficient titer of polyclonal antibodies that specifically react with IL-12, would have terminated the immunization schedule and sacrificed the animal. Thus, using standard techniques, further multiple immunizations would not have been done and antibodies specific for the 30-35 kD subunit would not have been made.

Benjamin Dec., ¶ 15.

This evidence shows that on skilled in the art would not have performed multiple immunizations because once a sufficient titer of polyclonal antibodies that specifically react with IL-12 were obtained, there would have been no need to continue the experiment.

8. Since The '945 Application Teaches That IL-12 Is A Homodimer Of The 40 kD Subunit, There Would Have Been No Reason To Perform The Multiple Immunizations Proposed By The Examiner

The Office Action states (p. 6):

> Applicants argue that one skilled in the art upon observing that immunized animals produced a sufficient titer of polyclonal antibodies that specifically react wit [*sic*, with] IL-12 would have terminated the immunization schedule and sacrificed the animal. However, contrary to Applicants arguments, if the Western blot analysis demonstrated that the polyclonal antibodies obtained reacted with the p40 subunit, one of skill in the art at the time of the earliest Trinchieri application, would have been motivated to further immunize the animal with the p70 heterodimer to obtain antibodies to the p35 subunit or to screen more hybridomas to obtain monoclonal antibodies to the p35 subunit because the state of the art at the time of the invention was such that working examples to demonstrate such were not required in the specification as filed.

The Examiner contends that upon observing that only antibodies that specifically react with the 40 kD subunit were obtained, one skilled in the art would have performed multiple immunizations and additional hybridoma screening to identify antibodies that specifically react with the 30-35 kD subunit. This contention ignores the teaching in the '945 application itself that IL-12 is a homodimer of the 40 kD subunit:

> These results indicate that the native NSF is a disulfide-bonded dimer (apparently a homodimer) of an approximately 40 kD species . . . .

'945 application, p. 26, ll. 5-7. Thus, the '945 application does not even acknowledge that a 30-35 kD protein exists as a subunit of IL-12 (much less disclose the amino acid sequence of that subunit).

Surely, one skilled in the art as of November 10, 1988 would not have even attempted to isolate an antibody to the 30-35 kD subunit because the '945 application teaches that IL-12 is a dimer of the 40 kD subunit only. Consequently, once a sufficient titer of anti-IL-12 antibodies was observed there would have been no motivation to perform multiple immunizations, and no antibodies that specifically react with the 30-35 kD subunit would have been sought or obtained.

C. Applicants Agree With The Examiner That There Is No Disclosure In The '945 Application To Selectively Purify IL-12 Heterodimer From The Free 40 kD Subunit

The Office Action states (pp. 6-7):

> Applicants argue that from the disclosure of the '945 application, there would have been no utility in purifying IL-12 because the IL-12 heterodimer and the free 40 kD subunit would have not been distinguished. However, contrary to Applicants arguments, the '945 application states that the NKSF polypeptides are used in the development of monoclonal and polyclonal antibody generation which antibodies are to be used diagnostically or therapeutically. *There is no mention in the disclosure of the use of the antibodies to selectively purify IL-12 heterodimer from the free 40 kD subunit*, as argued by Applicants. Therefore, Applicants arguments that none of the antibodies in the '945 application would have been able to selectively purify IL-12 heterodimer from free 40 kD subunit are unpersuasive because the use of the antibodies as disclosed in the '945 application were for diagnostic or therapeutic purposes, not to purify the IL-12 heterodimer. The state of the art at the time of the '945 application was that antibodies could be generated against the p70 heterodimer or p40 alone. Furthermore, as discussed above, multiple immunizations with the p70 heterodimer would have resulted in the production of antibodies to the p35 subunit (emphasis added).

This paragraph of the Office Action addresses Applicants' position that there was no utility for the claimed antibodies in selectively purifying IL-12 heterodimer from the 40 kD subunit because those molecules would not be separated. Since the Examiner agrees with Applicants that there is no disclosure in the '945 application of the use of the antibodies to selectively purify IL-12 heterodimer from the free 40 kD subunit, and that use in any event is not obvious, the issue has been mooted.

D. The Examiner Has Failed To Rebut Applicants' Position That There Is No Utility Disclosed In The Trinchieri '945 And '817 Applications For The Claimed Antibodies

1. The Examiner Has Applied The Wrong Legal Analysis

The Office Action states (pp. 7-8):

> With respect to *Applicants arguments that the Trinchieri '945 and '817 applications fail to describe any specific diagnostic or therapeutic use for antibodies that react with NKSF*, this argument is also unpersuasive. The Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Nevertheless, in the instant case not everything necessary to practice the claimed invention need be disclosed. In fact, what is well-known is best

> omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the knowledge and skill in the art. Section 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most clearly connected". The amount of guidance or direction present refers to information in the application that teaches how to make or use the invention, the amount of guidance or direction needed to enable the invention being inversely related to the amount of knowledge in the state of the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970) (emphasis added).

This paragraph of the Office Action sets forth the Examiner's view of the legal standards to be applied in assessing Applicants' argument that the Trinchieri '945 and '817 applications fail to describe any specific diagnostic or therapeutic use for antibodies that specifically react with IL-12. All of the three cases cited by the Examiner relate to enablement under 35 U.S.C. § 112, not disclosure of a practical utility under 35 U.S.C. § 101. While it is true that an application that fails to disclose a practical utility where there is no obvious utility also fails to teach "how to use" the claimed invention, case law generally considers the issue as a Section 101 issue, not an enablement issue. In any event, the enablement cases cited by the Examiner do not address the issue here: did either of the Trinchieri applications *disclose* a utility sufficient to meet Section 101.

For the proper analysis of the utility issue, Applicants refer to their Response, at pp. 28-31.

2. The Examiner Has Failed To Show Where The Prior Art Or Trinchieri Applications Disclose A Specific Utility For The Claimed Antibodies

The Office Action states (p. 8):

> In the instant case, the relative skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the Trinchieri '945 and '817 applications were filed, was such that *it was unnecessary for the specification to disclose what was well-known in the art and already available to the public (i.e. the diagnostic and therapeutic use for antibodies that react with NKSF).* A lot was known in the prior art about the nature of the invention and details as to how to make and use the invention were not required in order for the instant specification to be enabling (emphasis added).

It is the Examiner's position that it was not necessary for the '945 or '817 applications to disclose "what is known in the art and already available to the public (i.e. the diagnostic and therapeutic use for antibodies that react with NKSF [IL-12])." The Examiner also contends that "[a] lot was known about the nature of the invention and details as to how

to . . . use the invention [such that they] were not required in order for the instant specification to be enabling."

First, Applicants emphasize that the issue raised here is not enablement, as discussed by the Examiner, but whether the '945 or '817 applications contain a disclosure of a practical utility for the claimed antibodies.

Second, while the Examiner claims that "the diagnostic and therapeutic use for antibodies that react with [IL-12]" was well known in the art and already available to the public as of the filing dates of those applications, *absolutely no evidence is presented by the Examiner to identify those diagnostic and therapeutic uses* for the claimed antibodies! If it was so well known, then the Examiner should be able to point to where in the Trinchieri applications or the prior art the answers the following questions can be found:

(i) What disease or condition can be diagnosed with the claimed antibodies?

(ii) What disease or condition can be therapeutically treated with the claimed antibodies?

Unless the Examiner can demonstrate where those questions are answered in the prior art (*i.e.*, before November 10, 1988 for the '945 application, and before February 7, 1989 for the '817 application) or in the applications themselves, the Examiner's position fails. Therefore, Applicants respectfully request the Examiner to document for the record where there is disclosure in the prior art or in the Trinchieri applications of any disease or condition that can be diagnosed with or therapeutically treated with antibodies that specifically react with IL-12. If the Examiner cannot do so, then (a) Trinchieri is not entitled to the filing dates of either the '945 or the '817 application and (b) all claims of the '523 patent are unpatentable under 35 U.S.C. § 101 for failure to disclose a practical utility.

E. Applicants Agree That Stern *et al.* (1990) Is Prior Art Only If Trinchieri Is Not Entitled To Benefit Of The '945 And '817 Applications

The Office Action states (p. 8):

> Applicants argue that a publication by Stern et al. (1990) which discloses polyclonal and monoclonal antibodies to CLMF and the 40 kD subunit anticipates claims 1, 2, 4 and 6 of the '523 patent but is not prior art to Applicants captioned application. However, contrary to Applicants arguments, the Stern et al. publication is not prior art to the '523 patent because the earliest priority date of the '523 patent is 11/10/1988 due to filing of the '945 application.

Applicants do not contest that Stern *et al.* is prior art only if Trinchieri is denied benefit of the '945 and '817 applications. Moreover, the Examiner has not contested that claims 1, 2, 4 and 6 of the '523 patent are unpatentable if such benefit is denied.

F. Trinchieri's '945 And '817 Applications Do Not Have Written Description For Claims That Recite "Murine" or "Human" Antibodies

The Office Action states (pp. 8-9):

> With respect to claims 4, 5, of the Trinchieri '523 patent, Applicants argue that the '523 patent lacks written description of any "murine antibody" or "human antibody" since there is no mention of such subject matter in the patent. However, contrary to applicants arguments, the making of humanized as well as murine antibodies were well known in the art at the time of filing of Trinchieri's earliest application (11/10/88) and standard techniques would have been used to generate such antibodies. The Examiner has cited Jones et al. (1986), Liu et al. (1987), Verhoeyen et al. (March, 1988) and Tan et al (1985) for the proposition that human and murine antibodies could be constructed without having to resort to undue experimentation and were not beyond the state of the art at the time the '817 and '945 applications were filed. Therefore, the '817 and '945 Trinchieri applications are enabling for murine and human antibodies to IL-12 as claimed in the '523 patent.

This paragraph of the Office Action addresses Applicants' position that there is no written description in either the '945 or '817 applications for "murine" or "human" antibodies. The Examiner again applies the legal standard for enablement, not written description, and therefore arrives at the incorrect conclusion. Note that the Examiner's analysis" is based on (a) "the making of humanized as well as murine antibodies were well known in the art at the time of filing . . ." and (b) "standard techniques would have been used to generate such antibodies." In fact, the Examiner cited three references, Jones *et al.*, Liu *et al.*, Verhoeyen *et al.* and Tan *et al.* for the proposition that human and murine antibodies could be constructed without undue experimentation and were not beyond the state of the art at the time the Trinchieri applications were filed. Tellingly, the Examiner stated: "Therefore, the '817 and '945 applications *are enabling for murine and human antibodies* to IL-12 as claimed in the '523 patent" (emphasis added).

Clearly, the Examiner evaluated the issue as being enablement, while the issue raised by Applicants is written description. Under the applicable law of written description (see Request, pp. 28-31), Trinchieri's failure to describe murine or human antibodies to IL-12 leads to the conclusion that such subject matter cannot be claimed. In *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (C.C.P.A. 1967), the Court denied for lack of written description a

claim to a single compound that was not explicitly described but was within a disclosed genus that encompassed "something like a half million compounds." 379 F.2d at 993, 154 USPQ at 121. The Court commented:

> Specific claims to single compounds require reasonably specific supporting disclosure and while . . . *naming* is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required. Surely, given time, a chemist could name . . . all of the half million compounds within the scope of the broadest claim, which claim is supported by the broad disclosure. This does not constitute support for each compound individually when separately claimed.

379 F.2d at 994, 154 USPQ at 122.

Trinchieri's '945 and '817 applications merely describe the broad genus of "antibodies" generally. No particular species of animal antibodies is even mentioned. Clearly, the genus of all animals is vast. For the same reasons the Court in *Ruschig* denied a claim to a single species of compound where that compound was undisclosed but within a vast genus of compounds, so too here should Trinchieri be denied claims to murine and human antibodies because they are not disclosed and are merely within the vast genus of all animal antibodies. For these reasons, the '945 and '817 applications lack written description for claims 4 and 5, so priority benefit of those applications should be denied for those claims.

G. While The '945 And '817 Applications Disclose A Seven Amino Acid Peptide Within The 30-35 kD Subunit, That Does Not Mean Standard Techniques Would Generate Antibodies To The 35-35 kD Subunit

The Office Action states (p. 9):

> Applicants argue that the '945 application of Trinchieri discloses six peptides each ranging from five to eight amino acid residues in length ('945 application, page 27, lines 5-10). Applicants also argue that peptides 4, 5 and 6 correspond to the 35 kD subunit and that in the '817 application of Trinchieri, at positions 7 and 11 there were 2 mistakes in this amino acid sequence (see Benjamin Dec. Para 21). However, contrary to Applicants arguments, fragment number 6 (peptide 6) in the '945 application is a seven amino acid peptide which according to Harlow and Lane (cited by Applicants) as a synthetic peptide would suffice to produce antibodies to a protein containing that sequence. Therefore, even though the '945 application does not specifically teach the presence of a 35 kD subunit, the recitation of the seven amino acid peptide present in the 35 kD subunit, would suffice to produce antibodies to the 35 kD subunit.

Applicants agree with the Examiner's statement that the '945 and '817 applications disclose a seven amino acid peptide within the 30-35 kD subunit. However, that

does not assure that antibodies to the 30-35 kD subunit would necessarily be obtained using standard techniques. As stated by Dr. Benjamin (Benjamin Dec., ¶ 19):

> 19. It would have been difficult and uncertain as to whether one could elicit antibodies to a protein containing any of such peptides, even if the peptide were to be conjugated to a carrier protein. The quality and specificity of such antibodies would also be doubtful. Rather, a peptide of five to eight amino acids, generally, a peptide of at least approximately ten amino acids, would be used in generating antibodies. Thus, it would have been difficult and uncertain as to whether one could elicit antibodies specific for IL-12 using those peptides of the 30-35 kD subunit disclosed in the '945 application.

Dr. Benjamin makes two important points. First, it would have been difficult and uncertain whether one could generate antibodies to such peptides. Second, the quality and specificity of such antibodies would be doubtful. Consequently, one skilled in the art would likely not have used such a short sequence to attempt to produce antibodies that specifically react with the 30-35 kD subunit. As noted by Dr. Benjamin, generally a peptide of at least ten amino acids would be used. Thus, one skilled in the art would have waited until larger peptides (having, for example, one having ten amino acids) were identified before proceeding to immunize animals.

For these reasons, the Examiner's conclusion that one would necessarily obtain antibodies that specifically react with the 30-35 kD subunit using the seven amino acid peptide of the '945 application is not consistent with the evidence.

III. THE OBVIOUSNESS REJECTION OVER THE TRINCHIERI '523 PATENT

The Office Action states (p. 10):

> This rejection is maintained for reasons of record set forth at pages 3-4 of the previous Office action (Paper No. 5, 1/24/00) and on page 3 (Paper No. 15, 4/20/01) and for the reasons as set for the in paragraph 3 above.

Applicants' response to the obviousness rejection over the Trinchieri '523 patent is as follows. Because Applicants have demonstrated that the '523 patent is not entitled to the filing dates of either the '945 or '817 applications, its earliest effective date for purposes of 35 U.S.C. § 102(e) is, at best, September 18, 1990, which is after the earliest effective filing date (August 27, 1990, as noted below) for the captioned application. Therefore, the '523 patent is not available as prior art under Section 102(e) against the captioned application.

IV. THE EXAMINER HAS NOT CHALLENGED APPLICANTS' RIGHT TO BENEFIT OF THE AUGUST 27, 1990 FILING DATE OF THEIR '284 APPLICATION FOR PROPOSED COUNTS A AND B

Applicants demonstrated in their Request that they are entitled to the August 27, 1990 filing date of their '284 application for proposed counts A and B, *i.e.*, the subject matter of Applicants' claims 33-44. See Request, at pp. 43-46. The Examiner has not challenged Applicants' right to benefit of that application.

V. APPLICANTS RESPECTFULLY REQUEST THE EXAMINER TO RESPOND TO THE FOLLOWING ISSUES PRESENTED IN THEIR REQUEST

Applicants are concerned that a number of the positions they have raised have not been considered by the Examiner since they are not mentioned in the Office Action. Therefore, Applicants list below the major issued not discussed by the Examiner on which they would appreciate a response.

(i) At pp. 27-28 of their Request, Applicants argued that the '945 application does not disclose the *complete* amino acid sequences of either IL-12 subunit, so there can be no *written description* of any of claims 1-7, each of which recites the complete nucleotide sequence of at least one subunit. The Examiner appears to have considered the issue in the context of enablement and did not evaluate the *written description* issue with respect to the '945 application.

(ii) At p. 28 of their Request, Applicants argued that the '945 application teaches that IL-12 is a *homo*dimer of the 40kD subunit, so the application cannot have a written description of claims 1-5 and 7, which recite that IL-12 as a *hetero*dimer of the 40 kD subunit and the 30-35 kD subunits, or claims 3 and 7, which recite the 30-35 kD subunit.

(iii) At pp. 35-39 of their Request, Applicants argued that the '945 application fails to describe how to make antibodies to the 30-35 kD subunit, so there is no *written description* or enablement for claims 1, 3-5 and 7, which recite that subunit. The Examiner responded only to Applicants' enablement attack, but not their written description attack.

(iv) At pp. 39-40 of their Request, Applicants argued that the '817 application does not disclose the *complete* amino acid sequences of either IL-12 subunit, so there can be no *written description* of any of claims 1-7, each of which recites the complete nucleotide sequence of at least one subunit. The Examiner

appears to have considered the issue in the context of enablement and did not evaluate the *written description* issue with respect to the '817 application.

(v) At p. 40 of their Request, Applicants argued that the '817 application equivocates among the possibilities that IL-12 is a *hetero*dimer of the 40 kD and 30-35 kD subunits or a *homo*dimer of either subunit, so the application cannot have a written description for claims 1-5 and 7, which recite that IL-12 as a *hetero*dimer.

(vi) At pp. 42-43 of their Request, Applicants argued that the '817 application fails to describe how to make antibodies to the 30-35 kD subunit, so there is no *written description* or enablement for claims 1, 3-5 and 7, which recite that subunit. The Examiner responded only to Applicants' enablement attack, but not their written description attack.

(vii) At pp. 47-48 of their Request, Applicants argued that all claims of the '523 patent are unpatentable to Trinchieri for failure to disclose a practical utility for the claimed antibodies and how to use them. The Examiner did not analyze the utility/how to use issue with respect to the '523 patent itself.

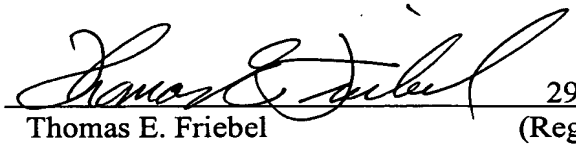
(viii) At p. 50 of their Request, Applicants argued that claims 4 and 5 of the '523 patent are unpatentable to Trinchieri for lack of written description for murine and human antibodies. The Examiner did not analyze the written description issue for the '523 patent itself.

CONCLUSION

Applicants respectfully request that the Examiner consider the above comments on the positions set forth in the Office Action. In addition, Applicants would appreciate responses to the additional issues listed in the preceding section that were raised in Applicants' Request, but not responded to by the Examiner. Prompt withdrawal of the outstanding rejections and declaration of an interference, as outlined in that Request, is respectfully solicited.

Respectfully submitted,

Dated: December 11, 2003



29,258
(Reg. No.)

Thomas E. Friebel
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036
(212) 790-9090